Amendments to the Specification

Please replace paragraph [0102] with the following replacement paragraph:

[0102] The association between markers was analyzed using Fisher's Exact test. ~~The software was available on the Simple Interactive Statistical Website which can be identified with a internet search using the terms "home.clara.net" (http://home.clara.net/sisa/index.htm).~~ For analysis of prognostic factors, we excluded 13 patients who did not receive therapy other than surgery. These patients had a poor performance status at the time of diagnosis and elected not to have further therapy. All other patients had received at least standard involved field fractionated radiation therapy. Kaplan-Meier curves were generated to assess the association of variables with time from initial diagnosis to evidence of progression by imaging or clinical features (time to tumor progression) and time from initial diagnosis to death (overall survival). To identify statistically significant differences in time to progression and overall survival, the Wilcoxon two sample test was used.

Please replace the paragraph [0009] with the following replacement paragraph:

[0009] As disclosed herein, a series of PI3K/Akt pathway biomarkers associated with cancers such as glioblastoma multiforme can be examined using for example a series of antibodies such as phospho-specific antibodies. In typical methods, a mammalian cell such as a cell derived from a formalin fixed, paraffin embedded glioblastoma multiforme biopsy sample can be examined for evidence of PI3K/Akt pathway activation by examining a tissue sample containing this cell for the presence of: a phosphorylated S6 polypeptide (SEQ ID NO: 1); a phosphorylated mTOR polypeptide (SEQ ID NO: 2); a phosphorylated FKHR polypeptide (SEQ ID NO: 3); a phosphorylated AKT polypeptide (SEQ ID NO: 4); a phosphorylated ERK polypeptide (SEQ ID NO: 8); or decreased levels of expression of the PTEN polypeptide (SEQ ID NO: 5), wherein the presence of a phosphorylated S6, mTOR, FKHR, AKT or ERK polypeptide, or decreased levels of expression of the PTEN polypeptide, provides evidence of Akt pathway activation in the glioblastoma cell. Optionally the cell is examined for the presence of a plurality of characteristics such as a phosphorylated S6 polypeptide (SEQ ID NO: 1) and decreased levels of expression of the PTEN polypeptide (SEQ ID NO: 5). Certain embodiments of the invention comprise further methodological steps, the step of using the results of the examination to identify and/or assess a therapeutic agent that may be used to treat the glioblastoma such as the step of using the results of the examination to evaluate the effect of an mTOR inhibitor such as ~~rapamycin~~ rapamycin or an analogue thereof or an EGFR inhibitor such as ZD-1839 or an analogue thereof on a glioblastoma cancer cell.

Please replace the paragraph [0054] with the following replacement paragraph:

[0054] Typically, the methods of the invention are used in evaluating the whether a tumor such as a glioma is likely to respond (i.e. is likely to exhibit growth inhibition) when contacted with an mTOR inhibitor or an EGFR inhibitor. In such

embodiments, the presence and/or phosphorylation status of a biomarker polypeptide that is associated with the activation of a pathway (e.g. a phosphorylated S6 ribosomal polypeptide (SEQ ID NO: 1)) is examined to determine if the pathway is disregulated in that tumor and is therefore susceptible to inhibition by [[a]] an inhibitor known to target that pathway. In such embodiments, the tumor is examined prior to its exposure to the inhibitor. Alternatively, the methods evaluate whether a tumor such as a glioma is responsive (i.e. exhibits growth inhibition) to an mTOR inhibitor or an EGFR inhibitor. In such embodiments, the activity of a biomarker polypeptide that is associated with the activation of a pathway (e.g. a phosphorylated S6 ribosomal polypeptide (SEQ ID NO: 1)) is examined after the tumor is exposed to the inhibitor to determine if the biomarkers in the pathway respond to exposure to the inhibitor.

Please replace the paragraph [0077] with the following replacement paragraph:

[0077] Embodiments of the invention also include articles of manufacture and/or kits designed to facilitate the methods of the invention. Typically such kits include instructions for using the elements therein according to the methods of the present invention. Such kits can comprise a carrier means being compartmentalized to receive in close confinement one or more container means such as vials, tubes, and the like, each of the container means comprising one of the separate elements to be used in the method. For example, one of the container means can comprise one or more of the antibodies disclosed herein (an anti-S6 antibody for example) that is or can be detectably labeled with a marker. For kits which utilize[[s]] immunological methods (e.g. immunohistochemistry and Western blotting) to detect the target proteins, the kit can also have containers containing buffers for these methods and/or containers comprising antibodies labelled with a reporter-means, such as a chromophore or radioactive molecule. In addition, for kits which utilize additional methodologies such as caspase-3 assays or tunel assays of apoptosis additional reagents associated with these techniques can be further included in the kits.

Please replace paragraph [0085] with the following replacement paragraph:

[0085] Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute[[®]] Cell Distribution Center, San Diego, California and the American Type Culture Collection, Rockville, Maryland. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor, J. Immunol., 133:3001 (1984); Brodeur *et al.*, Monoclonal Antibody Production Techniques and Applications, Marcel Dekker, Inc., New York, (1987) pp. 51-63).

Please replace paragraph [0087] with the following replacement paragraph:

[0087] After the desired hybridoma cells are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods (Goding, supra). Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells may be grown *in vivo* as ascites in a mammal. The monoclonal antibodies

secreted by the subclones may be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose® (GE Healthcare Bio-Sciences, Sweden), hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

Please replace paragraph [0098] with the following replacement paragraph:

[0098] Sections from the tissue microarray were stained with monoclonal antibodies to PTEN (clone 6H2.1, Cascade Bioscience, Winchester MA), EGFR (clone 31G7, Zymed®, San Francisco, CA), EGFRvIII (clone L8A4, a generous gift from Dr. Darrell Bigner), and phosphorylation specific antibodies directed against p-Akt (ser 473) p-FKHR (thr24) /p-FKHRL1 (thr32), p-mTOR (ser 2481), p-S6 ribosomal protein (ser 235/236) and p-44/42 MAP kinase (p-Erk) (thr202/tyr204) (Cell Signaling ~~Technologies~~ Technology®, ~~Beverly~~ Danvers, MA). Sections were baked at 60°C and de-paraffinized with xylenes and graded ethanols. Heat-induced antigen retrieval was used as follows: for p-Erk, p-Akt, p-mTOR, p-FKHR/FKHRL1 and p-s6, 0.01 M citrate buffer, pH 6 for 25 minutes in a pressure cooker; for PTEN, 0.01M citrate buffer, pH 6 for 16 minutes in a microwave oven; EGFR, pronase (0.03 g/ml of 0.05 M Tris buffer, pH 7.4) at 37°C for 8 minutes and for EGFRvIII, 0.01 M citrate buffer, pH 6 for 25 minutes in a vegetable steamer. Endogenous peroxidase activity was quenched with 3% hydrogen peroxide in methanol. Primary antibodies (PTEN at 1:400, EGFR at 1:150, EGFRvIII at 1:400, p-Akt 1:50, p-mTOR 1:50; p-FKHR/FKHRL1 1:50, pS6 1:50 and p-ERK at 1:50) were diluted in Tris buffered saline with 0.1% Tween and applied for 16 hours at 4°C, followed by anti-mouse or anti-rabbit biotinylated immunoglobulins (produced by VECTOR® Laboratories, Burlingame CA) at 1:100 dilution for one hour, and finally, avidin-biotin complex (ELITE® and ABC® complexes produced by, Vector® Laboratories) for one hour. Negative control slides received normal mouse serum (produced by DAKO®, Copenhagen, Denmark) as the primary antibody. Diaminobenzidine tetrahydrochloride was used as the enzyme substrate to visualize specific antibody localization for PTEN, EGFR and EGFRvIII; VECTOR® ~~NovaRed~~ NovaRED™ ~~(Vector) was used for~~ phospho-specific antibodies were utilized. Slides were counterstained with Harris hematoxylin.